

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)	MAIL STOP: APPEAL BRIEF-
Ming-Bo Wang et al.)	PATENTS
Application No.: 09/287,632)	Group Art Unit: 1635
Filed: April 7, 1999)	Examiner: JANE J ZARA
For: METHODS AND MEANS FOR)	Confirmation No.: 6526
OBTAINING MODIFIED PHENOTYPES)	Appeal No: _____

REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 41.41, Appellants present this reply to the Examiner's Answer dated July 7, 2010. Consideration of the following remarks and arguments in addition to the arguments and evidence relied upon in the Appeal Brief filed April 8, 2010 is respectfully requested.

TABLE OF CONTENTS

I.	Related Proceedings	1
II.	Argument.....	1
A.	Written Description	1
1.	The Examiner's Allegation	2
2.	Appellants' Specification Supports the Claimed Invention, Including the Element that the Examiner Now Complains About	3
a.	Appellants' Specification Has Literal Support for the Full Range of the Invention Recited in the Claims.....	3
b.	Appellants' Specification Provided More Extensive Working Examples Than the Examiner has Acknowledged.....	4
c.	Appellants' Appeal Brief Provided Further Testimonial and Circumstantial Evidence of the Adequacy of the Written Description.....	5
d.	The Examiner Has Provided Neither Evidence nor Authority to Support the Alleged Basis of the Rejection	6
B.	Obviousness.....	8
1.	Fire, Brown, Lusky, Scheidner and Barracchini.....	8
2.	Flavell, Metzloff et al., Stam et al., Brown et al., and Lusky et al.....	12
C.	Double Patenting	16
III.	Conclusion.....	16

I. Related Proceedings

The Appellants' legal representative, or assignee, does not know of any other appeal or interference which will affect or be directly affected by or have bearing on the Board's decision in the pending appeal. Appellants note the following matters which may be of interest to the Board.

At the time that the appeal was taken, a suggestion of interference pursuant to 37 C.F.R. § 41.202 had been filed in related co-pending application 11/364,183. Interference No. 105,754 has now been declared between related U.S. Patent Application No. 11/364,183 and U.S. Patent Nos. 6,506,559 and 7,622,633 by Fire et al.

An appeal has been filed in the reexamination of U.S. Patent No. 6,573,099, which is not directly related to the present application, but is owned by the same real party in interest. The reexamination is being conducted under application numbers 90/007,247 and 90/008,096 (merged). An Oral Hearing has been held in that appeal.

II. Argument

Appellants' Appeal Brief set forth sufficient reasons to overturn the rejections of record in this application. The Examiner's Answer has reiterated those rejections. The Examiner has not fully addressed Appellants' arguments and has not remedied the deficiencies in the rejections which Appellants previously identified. Below, Appellants address specific allegations by the Examiner in the Examiner's Answer.

A. Written Description

At pages 4-8 of the Examiner's Answer, the Examiner has reiterated the rejection of claims 22, 26, 42, 53, 54, 56, 58, 63-69, 100-103, 109, 115-122 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In the paragraph bridging pages 4-5, the Examiner has broadly alleged that the claims contain

subject matter which was not described in the specification in such a way to reasonably convey that appellants were in possession of the claimed invention. In the paragraph bridging pages 5-6 the Examiner generally alleged that the claims are directed to a broad genus.

Appellants' Appeal Brief rebutted the Examiner's assertions with charts and explanation demonstrating exemplary description of every element of the claimed invention in the specification. APPEAL BRIEF at 12-13 and 22-28. Appellants also rebutted particular prior allegations with testimonial and circumstantial evidence that persons of ordinary skill would have, and indeed actually have, recognized that the inventors were in possession of a broad generally useful invention. APPEAL BRIEF at 14-21.

1. The Examiner's Allegation

The Examiner's allegations have evolved with each reiteration. The allegations presented in the Examiner's Answer appear to be principally concerned with the length of the portion of the construct that is complementary to a target sequence. Specifically, the Examiner alleged that

The instant rejection is directed to eukaryotic cells and plants comprising RNAi constructs that comprise lengths as small as 20 nucleotides that are fully complementary and target a nucleic acid capable of being phenotypically expressed.

EXAMINER'S ANSWER at 6, lines 6-9.¹ Further, the Examiner alleged that

Applicants did not have support, prior to Fire's disclosure, for the limitations instantly claimed, particularly with respect to siRNA of lengths as short as 20 nucleotides in length per strand.

EXAMINER'S ANSWER at 28, lines 16-19. Thus the Examiner's current principal complaint appears to concern Appellants support for the claimed subject matter at the lower bound of

¹ It should be noted that the claims on appeal include claims encompassing plant cells, not eukaryotic cells generally. Therefore, the Examiner has not properly construed the claims in maintaining the rejection.

the size of the targeting sequence portion of the claimed constructs.

The Examiner contends that because the sense and anti-sense sequences in the working examples of Appellants' disclosure were generally longer than the lower bounds recited in the claims that Appellants were not in possession of the invention as claimed. However, the Examiner's allegations do not fully account for the content of Appellants' disclosure.

**2. Appellants' Specification Supports the Claimed Invention,
Including the Element that the Examiner Now Complains About**

Appellants' specification contains both literal support and more extensive working examples of the claimed invention than the Examiner has acknowledged.

**a. Appellants' Specification Has Literal Support for the Full
Range of the Invention Recited in the Claims**

Appellants' disclosure contains explicit literal written description covering the range of lengths of sense and antisense sequence elements recited in the claims. Indeed, the Appeal Brief identified exemplary description of every element of the claims. APPEAL BRIEF at 12-13, 22-28. The Examiner's Answer does not properly address the literal support in the specification for each and every element of the claims.

As for the particular aspect that the Examiner now complains about, a sense nucleotide sequence including at least 20 consecutive nucleotides having 100% sequence identity with at least 20 consecutive nucleotides of the nucleotide sequence of a nucleic acid of interest is described for example at p. 15, ll. 9-23, p. 17, ll. 28-30, and p. 20, l. 18 to p. 21, l. 11 and shown in the examples. An antisense nucleotide sequence including at least 20 consecutive nucleotides having 100% sequence identity with the complement of said at least 20 consecutive nucleotides of said sense nucleotide sequence is described, for example at p. 21, ll. 12-18 and shown in the examples.

The Examiner has provided no evidence that a person of ordinary skill in the art would not have recognized that the inventors had described sense and antisense sequences corresponding to the recited range limitations of the claims.

b. Appellants' Specification Provided More Extensive Working Examples Than the Examiner has Acknowledged

The Examiner has acknowledged that the Appellants' disclosure provides more than one working example of the claimed invention. EXAMINER'S ANSWER at 6. The Examiner has acknowledged that Appellants' disclosure described working examples within the claimed range. In particular, the Examiner has acknowledged that the specification provides at least two working examples, a construct targeting a Gus gene (of approximately 1580 base pairs) and a construct for reducing expression of a delta 12 desaturase gene (of approximately 620 base pairs). EXAMINER'S ANSWER at 6.

However, the working examples of the specification are more extensive than the Examiner has acknowledged. Pages 35-38 of the specification described constructs targeting Gus having about 558 bases identical with the target, targeting protease (Pro) of PVY with about 1295 bases identical to the target and targeting delta 12 desaturase with about 480 bases identical to the target. Therefore the Examiner's acknowledgment of the Appellants' disclosure did not even fully acknowledge the working examples presented in Appellants' disclosure.

c. Appellants' Appeal Brief Provided Further Testimonial and Circumstantial Evidence of the Adequacy of the Written Description

Appellants have also submitted extensive expert testimony. Appellants submitted the declarations of Dr. Elizabeth Salisbury Dennis (EXHIBIT 19)² and Dr. Marc de Block (EXHIBIT 20). Dr. Dennis testified that

[A] person of ordinary skill in the art would have concluded, judging at the filing date of the Application, that the Application adequately described all of the necessary features of the claimed subject matter in a manner sufficient to convey that the inventors were in possession of the invention as presently claimed.

DECLARATION OF DR. ELIZABETH SALISBURY DENNIS (EXHIBIT 19) at ¶ 18. Dr. De Block also testified that “the Application adequately described the claimed subject matter, to convey that the inventors were in possession of the invention as broadly claimed.” DECLARATION OF DR. MARC DE BLOCK (EXHIBIT 20) at ¶ 18.

These experts testified to the general adequacy of Appellants disclosure from the viewpoint and knowledge of persons of ordinary skill. An additional declaration by Dr Peter Schofield (EXHIBIT 21) was submitted. Dr. Schofield testified that

Given the general applicability of the teachings of the specification to any potential target gene and any intron, it is my opinion that the '632 application sufficiently described the full range of chimeric DNA constructs recited in the claims. A person of ordinary skill would have recognized that the teachings of the specification could be practiced with more than a sufficient number of known nucleic acid sequences of interest (i.e. target genes) and intron sequences to be representative of the genus as a whole. Therefore, I believe that a person of ordinary skill in the filed would have recognized that the applicants were in possession of the full scope of the claimed genus at the time the application was filed.

Declaration of Dr Peter Schofield (EXHIBIT 21) at ¶ 30. Appellants further submitted the declaration of Dr Michael Metzloff (EXHIBIT 22), stating his opinion that the application

² References to Exhibits throughout this Reply Brief are references to the Exhibits provided in the Evidence Appendix of the Appeal Brief. No new evidence is relied upon.

described the invention in sufficient detail to demonstrate that the inventors had a complete conception of the invention and described it sufficiently such that a person of ordinary skill in the art would have understood what the invention was and how it was distinguished over the prior art. DECLARATION OF METZLAFF (EXHIBIT 22) at 4, ¶ 14.

Finally, Appellants have presented evidence from the scientific literature that the disclosure of Appellants' experimental examples were recognized as having general applicability. Appellants' invention has been widely adopted by persons of skill in the art on the basis of Appellants' examples. Those who have adopted the invention, have cited the Appellants' scientific publication, Smith et al. 2000, *Nature*, 407, 319-320 (EXHIBIT 9), as forming the basis of their own constructs. See Exhibits 10-18. For example, Exhibits 10-18 represent a sample of the publications that give due credit to the scientific publication of the same examples disclosed in the present specification as providing disclosure leading to widespread general manufacture and use of Appellants claimed constructs. The wide adoption of the invention and citation of the Appellants' publication of the examples of the specification is further circumstantial evidence that persons of ordinary skill in the art viewed the inventors as having created an invention of general applicability.

For at least the reasons set forth in Appellants' Appeal Brief, the rejection of claims 22, 26, 42, 53, 54, 56, 58, 63-69, 100-103, 109, 115-122 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement should be overturned.

d. The Examiner Has Provided Neither Evidence nor Authority to Support the Alleged Basis of the Rejection

The Examiner has not identified any scientific evidence that the working examples presented in the disclosure are not adequately representative of the invention at the lower bound of sequence lengths. In the absence of any evidence of particular unpredictability with

respect to the utility of the claimed invention using sense and antisense lengths between those exemplified in the example and the lower limits recited in the claims, there is no scientific basis for the Examiner's contentions.

At pages 8 and 31 of the Examiner's Action, the Examiner refers to paragraph 14 of the Declaration of Marc De Block (EXHIBIT 20), alleging that the activity of certain constructs depended on the insertion of a particular intron. The Examiner implies that this demonstrates some deficiency of the written description. The Examiner has mischaracterized the testimony of Dr. De Block. His testimony indicates that he understood that the inventors were in possession of a broadly useful invention because the particular identity of the intron used in a construct such as recited in the claims is not important to achieve a result with any target gene. DECLARATION OF MARC DE BLOCK (EXHIBIT 20) at ¶ 17. In the paragraph cited by the Examiner, Dr. De Block compares the results of certain constructs without an intron with constructs including an intron to show that the intron provided for much more effective gene silencing phenotypes. DECLARATION OF MARC DE BLOCK (EXHIBIT 20) at ¶ 14. Thus, the Examiner's allegations as to the meaning of the Declaration of Marc De Block is incorrect.

The Examiner has cited no authority for her contention that an application must provide working examples at the outer bounds of a claimed genus. Indeed, controlling precedent makes clear that a patent claim is not invalid just because it is broader than the specific examples of the specification. *See Bilstad v. Wakalopulos*, 386 F.3d 1116, 1123 (Fed. Cir. 2004) (“We cannot agree with the broad proposition ... that in every case where the description of the invention in the specification is narrower than that in the claim there has been a failure to fulfill the description requirement in section 112.”) (*quoting In re Smythe*, 480 F.2d 1376, 1382 (CCPA 1973)); see also *Texas Instruments, Inc. v. Int'l Trade Comm'n*, 805 F.2d 1558, 1563 (Fed. Cir. 1986) (“This court has cautioned against limiting the claimed invention to preferred embodiments or specific examples in the specification.”).

Thus, there is no basis in either science or law for the Examiner's alleged complaint.

B. Obviousness

1. Fire, Brown, Lusky, Scheidner and Barracchini

At page 8-16 of the Examiner's Answer, the Examiner has reiterated the rejection of claims 22, 26, 42, 53-54, 56, 58, 63-69, 100-103, 109, and 115-122 under 35 U.S.C. § 103(a) as allegedly unpatentable over Fire et al. (US 6,506,559) in view of Brown et al. (US 5,859,347), Lusky et al. (US 6,350,575) and Schiedner et al. (Nature Genetics, 18:180-83, 1998), the combination in view of Baracchini et al. (US 5,801,154).

Although the Examiner has acknowledged that Fire et al. does not teach or suggest all the elements of the claimed invention, Appellants submitted a Declaration by the Inventors under 37 C.F.R. § 1.131 (Exhibit 23) with the Amendment filed May 1, 2008. The declaration presents evidence that the invention was actually reduced to practice prior to the December 23, 1997 filing date of U.S. provisional application No. 60/068,562 for which benefit is claimed by Fire et al. (U.S. Patent 6, 506, 559).

At page 10 of the Examiner's Answer, the Examiner has contended that the Declaration by the Inventors under 37 C.F.R. § 1.131 was insufficient because the declaration did not demonstrate an actual reduction to practice of an embodiment at the lower size limit of the claimed invention. In particular, the Examiner has alleged that:

Applicant has not provided proper support [in the Declaration by the Inventors] for the size limitations instantly claimed to exclude Fire as prior art. . . . Applicant has not provided proper support [in the Declaration by the Inventors] for the short nucleobase size limitations of the instant claims, which are drawn to RNAi constructs comprising at least 20 nucleotides in length. Support has been provided for double stranded constructs comprising more than 550 nucleotides in length, but not comprising 20 nucleotides in length.

Examiner's Answer at 10.

The Examiner has fundamentally misapplied the standard for the requirements to antedate a reference. Appellants have previously pointed out that in *In re Clarke*, the Court explained:

If the question of how much need be shown in antedating affidavits is cast in terms of *support* for the *claims*, then an applicant would be required to show as much as is required by 35 U.S.C. 112 to *support* a generic *claim*. However, we think such analysis in terms of support for the claims to be erroneous and improper here. We would add that an analysis in terms of the law involving “genus” and “species” does not promote a disposition of the issue here.

In re Clarke, 148 U.S.P.Q. 665, 669-70 (C.C.P.A. 1966). Thus, it is old law that antedating affidavits need not show the full scope of a claimed genus, but rather “antedating affidavits must contain facts showing a completion of ‘the invention’ commensurate with the extent the invention is shown in the reference.” *Id.*

Fire et al. does not disclose all the elements of the invention. Moreover, contrary to the Examiner’s characterization, Fire et al. does not disclose RNAi constructs as short as 20 nucleotides. The examples of Fire et al. range from 299 to 1033 nucleotides in length. Fire et al. (U.S. Patent No. 6,506,559) at col. 23. The declaration of the inventors demonstrated multiple complete actual reductions to practice of the invention, including within the range of RNAi sizes disclosed by Fire et al., prior to the effective date of the reference.

Moreover, it should be noted that the *Clarke* court went on to explain that priority need not always be shown by a direct one-to-one antedating of the specific disclosure of a reference. When the species of the generic invention that has been completed prior to the effective date of the reference would make obvious to one of ordinary skill in the art the species disclosed in the reference, the reference may be said to have been “indirectly antedated.” *In re Clarke*, 148 U.S.P.Q. at 669-70. The Examiner has asserted that Barrachini et al. would have rendered obvious targeting sequences of at least 10 nucleobases. By the Examiner’s own logic, the species disclosed in Appellants’ declaration would have rendered

obvious the use of targeting sequences of at least 10 nucleobases when considered in view of Barrachini et al. In any event, the examples of actual reduction to practice prior to the date of Fire et al. would have rendered the range of RNAi sizes disclosed by Fire et al. obvious.

Appellants have antedated the Fire et al. reference by proving actual reduction to practice of complete embodiments of the invention prior to the earliest disclosure of Fire's results and prior to the earliest possible effective date of the Fire application. Thus, Fire et al. is not effective prior art.

Moreover, even if Fire et al. were not removed, the Examiner has acknowledged that Fire et al. does not teach or suggest all the elements of the invention. Among the distinctions between Fire et al. and the presently claimed inventions, the Examiner has acknowledged that Fire et al. do not teach "RNAi expression constructs comprising an intron sequence." This is a feature recited in the claims under appeal.

As disclosed in the present application, Appellants discovered that inclusion of an intron in a hairpin dsRNA gene silencing construct provides surprisingly improved gene silencing. These findings were published in the scientific literature by the Appellants in Smith et al., *Nature*, 407:319-32, 2000 (Exhibit 9). The improved efficiency provided by the inclusion of an intron in the construct was not predicted by any cited reference. The improvement has been widely adopted in the art since the publication of Smith et al. A sample of papers that Appellants provided to the Examiner demonstrate that persons of ordinary skill in the art have widely adopted the use of hairpin dsRNA constructs comprising introns and have cited the work of the inventors in numerous reports. *See* EXHIBITS 10-18.

The Examiner cited each of Brown et al., Lusky et al., and Schiedner et al., in an attempt to remedy this deficiency of Fire et al. However each of these disclosures is limited to the specific circumstances taught therein, none of which provide a reason to modify Fire et al. as the Examiner has alleged would have been obvious. Baracchini et al. is cited in

attempting to remedy a different deficiency has no teaching at all concerning introns in recombinant constructs.

Brown et al. taught that a specific inclusion of an intron in an expression construct provided higher levels of protein expression. The purpose of the present invention is to suppress gene expression not enhance gene expression. There is no evidence and there would have been no reason to think that whatever mechanism by which the intron of Brown et al. promoted protein expression would have any effect on the efficiency of gene suppression by an artificial hairpin RNAi construct.

Lusky et al. taught viral vectors. Lusky et al. taught that the genetic material of viral vectors may comprise introns. However, Lusky et al. provides no reason at all to include an intron in construct expressing an artificial hairpin RNAi molecule.

Scheidner et al. taught the use of high capacity adenoviral vectors for gene therapy. The genetic material of these constructs might contain introns, but Scheidner et al. provides no reason to specifically include an intron in an artificial hairpin RNAi construct. To the extent that an intron might stabilize a high capacity adenoviral vector, such a teaching would be particular to the requirements of viral particle assembly and would have no bearing on the constructs recited in the claims under appeal.

Baracchini et al. is alleged to teach that targeting sequences may comprise at least 10 nucleobases. Baracchini et al. provides no reason to specifically include an intron in an artificial hairpin RNAi construct.

Because the primary reference has been antedated, the rejection should be overturned. Furthermore, even if the primary reference were not antedated, the Examiner has not identified one scientifically based reason to modify the primary reference so as to include an intron as recited in each of the claims on appeal. Thus, the rejection is unsupported in fact or law and should be overturned.

2. Flavell, Metzloff et al., Stam et al., Brown et al., and Lusky et al.

At pages 16-25 of the Examiner's Answer, the rejection of claims 22, 26, 42, 53-54, 56, 58, 63-69, 100-103, 109, and 115-122 under 35 U.S.C. § 103(a) as being unpatentable over Flavell (Proc. Natl. Acad. Sci., 91:3490-96, 1994) (Exhibit 6), Metzloff et al. (Cell, 88:845-54, 1997) (Exhibit 2) and Stam et al. (Annals of Botany, 79:3-12, 1997) (Exhibit 3), the combination in view of Brown et al., (US 5,859,347) (Exhibit 4), and Lusky et al. (US 6,350,575) (Exhibit 5) has been reiterated.

In the Examiner's Answer, the Examiner has acknowledged that:

The primary references of Flavell, Metzloff, and Stam do not teach double stranded hairpin constructs in their inverted repeats, nor do they teach the insertion of an intron in their double stranded inhibitory constructs.

EXAMINER'S ANSWER at 22; *see also*, OFFICE ACTION mailed September 19, 2008 at 7, last paragraph. That is to say, the Examiner has acknowledged that the primary references fail to teach the effect of double stranded RNA in RNA interference, the use of hairpin constructs, or the inclusion of an intron in an RNAi hairpin constructs, all essential novel features of the presently claimed invention as a whole. Nevertheless, the Examiner has contended that the combined teachings of the reference would have somehow led a person of ordinary skill in the art to the to presently claimed invention.

Further in the Examiner's Answer, the Examiner conjectures that:

Applicant logically extrapolated what was speculated in the plant literature for a decade, that long stretches of inverted repeats often coincided with plant co-suppression. That is where the teachings of Flavell, Metzloff and Stam become relevant as prior art, in providing the forethought that lead to the next logical experiment.

EXAMINER'S ANSWER at 41.

It is irrelevant how the inventors came to the insight which led to the present invention. 35 U.S.C. § 103 ("Patentability shall not be negated by the manner in which the invention was made."). What matters is whether a person of ordinary skill in the art would

have found the differences between the prior art and the invention to be obvious. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). One may scour the history of plant gene co-suppression literature for clues that might, in hindsight, have led to experiments that might have led others to the discovery of RNAi if only they had done one thing or another. However, while such an analysis might be of interest to science historians, it is not a proper basis for rejecting patent claims. It is impermissible to first ascertain factually what applicants did and then view the prior art in such a manner as to select from the prior art only those which may be modified and then utilized to reconstruct applicant's invention from such prior art. *See, e.g., Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 550 (Fed. Cir. 1985); *see also, In re Shuman*, 150 U.S.P.Q. 54, 57 (C.C.P.A 1966).

The fact is that the experiments that the Examiner has cited did not lead any person of ordinary skill to the present invention. A showing of surprising results, lack of predictability, and widespread adoption of the invention following its disclosure are all secondary considerations pointing to the fact that the invention was not obvious. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 15-17 (1966). Each of these are present in the claimed invention. The strongest possible objective evidence of non-obviousness has been conferred by the scientific community on the first publication to suggest the RNAi phenomenon. The announcement of the 2006 Nobel Prize in Physiology or Medicine states:

Fire and Mello published their findings in the journal *Nature* on February 19, 1998. Their discovery clarified many confusing and contradictory experimental observations and revealed a natural mechanism for controlling the flow of genetic information. This heralded the start of a new research field.

Nobelprize.org: The Nobel Prize in Physiology or Medicine 2006, Press Release of the Nobel Assembly at Karolinska Institute (October 2, 2006)(Exhibit 26); *see also* Fire A., Xu S.Q., Montgomery M.K., Kostas S.A., Driver S.E., Mello C.C., 1998, Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. *Nature*, 391:806-11

(Exhibit 26). In commentary published in the same issue as the Fire et al. *Nature* publication, Wagner and Sun described the reported effect of dsRNA targeting genes in *C. elegans* as “remarkable and surprising.” Wagner and Sun, *Nature*, 39:744-45 (1998) (EXHIBIT 24).

The Declaration of the Inventors under 37 C.F.R. § 1.131 (EXHIBIT 23) proves that the present invention was actually reduced to practice prior to the filing of the Fire et al. patent application and the publication which earned them the Nobel Prize.

Appellants have pointed out that the Examiner’s hindsight reconstruction is inconsistent with the issuance by the Office of U.S. Patent No. 6,506,559 to Fire et al. At page 40 of the Examiner’s Answer, the Examiner attempts to cover this apparent inconsistency with argument that Fire et al. discovered the use of short double stranded RNA fragments while the instant inventors demonstrated the use of longer constructs. This is an artificial distinction that is not made in the claims of the Fire patent. The Examiner’s contention is also factually incorrect. Contrary to the Examiner’s characterization, Fire et al. does not disclose short RNAi constructs. The examples of Fire et al. range from 299 to 1033 nucleotides in length. Fire et al. (U.S. Patent No. 6,506,559) at col. 23. A distinction between long and short double-stranded RNA was not made by contemporary commentators. *See, e.g.*, EXHIBIT 24. Such a distinction is also not evidenced in the commentary by others reflecting on the discovery, as represented for example by the Nobel Committee. *See, e.g.*, EXHIBIT 26. It is not the length of the constructs that the commentators found surprising and not obvious, rather it was the double stranded nature of the effective RNA molecule. Thus, the Examiner’s false distinction has no basis in the perspective of one of ordinary skill in the art at the time of the invention.

No amount of hindsight reasoning can overcome the overwhelming objective evidence that the scientific community considered the RNAi phenomenon surprising and non-obvious when it was first revealed after Appellants actual reduction to practice.

However, Appellants have also presented direct testimony from an expert who was active in the field at the time of the invention. Appellants also presented a declaration by Dr Michael Metzloff pursuant to 37 C.F.R. § 1.132 (Exhibit 22). Dr. Metzloff who is co-author of one of the primary references relied on by the Examiner contradicts the Examiner's interpretation of the state of the art at the time the invention was made. Dr Michael Metzloff testified that the publications by Flavell, Metzloff et al. and Stam et al (or other contemporaneous publications related to the field of co-suppression) did not contemplate that double stranded RNA structures formed between antisense RNA and the sense mRNA could be a triggering agent in gene silencing. DECLARATION OF METZLOFF at ¶ 9. Dr Metzloff also testified that a person of ordinary skill in the art would not have included a sense and antisense RNA strand in one single molecule because the proposed models and prevailing wisdom considered only an antisense strand to be the operative gene-silencing triggering molecule. He also testifies that as a person of at least ordinary skill at the time, he would never have contemplated deliberately introducing complimentary sense and antisense sequence of a target gene which can form a double stranded RNA molecule. DECLARATION OF METZLOFF at ¶ 9.

Appellants have shown through objective evidence that those of skill in the art considered the underlying discovery of RNA interference using dsRNA to be surprising and remarkable at the time it was first described, so much so that the first authors to publish on the subject were awarded the Nobel Prize. Appellants have demonstrated through affidavit that the present invention was completed prior to that first publication by Fire et al. or the filing of a patent application by Fire et al. Appellants have further proven through testimonial evidence that the Examiner's hindsight consideration of the state of the art does not accurately reflect the understanding of a person of ordinary skill at the time the invention was made. Rather, the prior art would not, could not, and did not render the invention

obvious to even an expert in the field (and an author of the cited prior art) at the time the invention was made.

Therefore, the allegations of the rejection are overwhelmingly refuted by the evidence of record. The rejection must be overturned and such action is respectfully requested.

C. Double Patenting

At pages 26-27 of the Examiner's Answer, the Examiner has reiterated the provisional rejection of claims 22, 26, 42, 53, 54, 56, 58, 63-69, 100-103, 109, and 115-122 under the doctrine of obviousness type double patenting over pending claims 35-38 of U.S. Patent Application No. 11/841,737. The Examiner has provided no direct response to Appellants' arguments in the Appellants' Appeal Brief.

Appellants maintain that the provisional rejection is improper for the reasons stated in the Appeal Brief.

III. Conclusion

Appellants' Appeal Brief set forth sufficient reasons to overturn the rejections of record in this application. For those reasons and as further argued above it is proper for the Board to overturn each of the Examiner's rejection and order that the application be permitted to issue without further delay. Such action is respectfully requested.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: September 7, 2010

By: /Christopher L. North/
Christopher L. North
Registration No. 50433

Customer No. 21839
703 836 6620